



61

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/46, 31/43		A1	(11) International Publication Number: WO 91/15197 (43) International Publication Date: 17 October 1991 (17.10.91)
<p>(21) International Application Number: PCT/GB91/00516</p> <p>(22) International Filing Date: 2 April 1991 (02.04.91)</p> <p>(30) Priority data: 9007945.0 7 April 1990 (07.04.90) GB</p> <p>(71) Applicant (<i>for all designated States except US</i>): BEECHAM GROUP PLC [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): MERRIFIELD, David, Roy [GB/GB]; SmithKline Beecham Pharmaceuticals, Clarendon Road, Worthing, West Sussex BN14 8QH (GB). CARTER, Paul, Laurence [GB/GB]; SmithKline Beecham Pharmaceuticals, Clarendon Road, West Sussex BN14 8QH (GB). DOUGHTY, David, George [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).</p>		<p>(74) Agent: WALKER, Ralph, Francis; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: PHARMACEUTICAL FORMULATION</p> <p>(57) Abstract</p> <p>A pharmaceutical formulation comprising an amoxycillin hydrate and an effervescent couple, for example citric acid plus sodium bicarbonate or sodium glycine carbonate, or tartaric acid or malic plus sodium carbonate. Potassium equivalents of these sodium salts may be used. The formulations may be free flowing powders or granules, or tablets.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MC	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America

-1-

PHARMACEUTICAL FORMULATION

The present invention relates to pharmaceutical compositions for oral administration in the treatment of bacterial infections.

In some clinical situations, to improve patient compliance, it is desirable to administer medicaments orally in liquid form as suspensions or solutions.

10

EP-A-0080862 (Beecham) discloses water-dispersible compositions of amoxycillin trihydrate, in which the amoxycillin trihydrate and other ingredients are formulated with a non-hygroscopic water-soluble binder.

15

Solutions are favoured over suspensions for oral administration, since drugs in solution are more rapidly absorbed. Solutions are also often more acceptable to patients, in terms of palatability. It has been proposed to 20 prepare dry effervescent formulations of medicaments in which, on addition to water, a medicament is dispersed in the water by the effervescing action and dissolves either as a result of the agitation or by interaction with components of the formulation. For example, GB-A-1287475
25 (Aspro-Nicholas) describes an effervescent formulation of aspirin. In order to obtain effective contact of the aspirin with the solubilising compounds during effervescence, the aspirin particles are pre-coated with a special readily wettable coating.

30

Effervescent formulations of antibiotics are disclosed in GB-A-1300998 (Biochemie). In this disclosure it is considered essential that the antibiotic is in the form of a water-soluble salt in the dry formulation. For amoxycillin 35 this would be disadvantageous because the water-soluble sodium salt is very hygroscopic and unstable when it has

-2-

absorbed water.

A dispersible tablet formulation containing amoxycillin is disclosed in EP-0281200-A1 (Gist-Brocades). This 5 formulation does not result in a clear solution of dissolved amoxycillin, but a suspension.

We have now discovered that amoxycillin that is not in salt form can be provided as an effervescent formulation in which 10 it is solubilised on contact with water, and in particular that will produce a clear solution for oral administration.

According to the present invention there is provided a pharmaceutical formulation comprising an amoxycillin hydrate 15 and an effervescent couple which comprises an acid component and an alkaline component, which generates carbon dioxide on contact with water, in which the alkaline component of the couple is present in excess of the stoichiometric equivalent of the acid component.

20

The amoxycillin hydrate is preferably amoxycillin trihydrate and may be provided in conjunction with a β -lactamase inhibitor, such as clavulanic acid or a salt thereof preferably potassium clavulanate. A suitable ratio range of 25 amoxycillin: clavulanic acid or clavulanate salt equivalent is 12:1 to 1:1, preferably 7:1 to 1:1, 4:1 to 1:1 or 2:1 to 1:1, by weight. A suitable proportion of amoxycillin in the formulation is 10-30% by weight, e.g. 10-25%.

30 The effervescent couple is preferably based on citric acid and sodium bicarbonate or sodium glycine carbonate, but other solid acid/carbonate couples may be used, for example tartaric or malic acid and sodium carbonate or potassium bicarbonate or mixtures of these acid and alkaline 35 components. The effervescent couple is provided in a sufficient amount to rapidly disperse and assist dissolution of the components of the formulation. The corresponding

-3-

potassium salts of the alkaline component may be used together with the sodium salts (or as a substitute) to avoid excessive levels of sodium ions. This may be necessary when high doses of amoxycillin are included in the composition.

5

The alkaline component should be present in sufficient amount to both neutralize the acid component and to solubilise the amoxycillin by formation of soluble e.g. sodium/potassium, salts. The aim is that the resulting 10 aqueous solution should have a pH of not less than 8 to achieve solubilization of amoxycillin trihydrate. Typically the composition may contain 50-75% of an alkaline component such as sodium or potassium hydrogen carbonate or glycine carbonate, by weight. A suitable mixed alkaline component 15 is a 3-1.5:1, for example 2.5-2:1 by weight mixture of sodium glycine carbonate: potassium bicarbonate.

Typically the composition may contain 2-25%, e.g. 5-20%, e.g. 5-17.5%, by weight of an acid component such as citric 20 acid.

The amounts of effervescent couple and excess alkaline component required to achieve rapid and complete solubilisation of a particular amoxycillin dosage can be 25 determined by simple experiments. For doses of amoxycillin of 1g or more, suitable ranges of molar ratios of sodium glycine carbonate: amoxycillin: potassium bicarbonate: citric acid in the formulation are 4-10: 1-3: 5-10: 1, for example 5-8: 1.5-2.5: 6.5-7.5: 1. Citric acid is tribasic, 30 and suitable molar ratios of other acids may be calculated accordingly. The suitable molar ratio expressed above corresponds to a weight ratio sodium glycine carbonate 4.8-12: amoxycillin 1.9-5.7: potassium bicarbonate 2-6-5.1: citric acid 1, with a preferred weight ratio of sodium 35 glycine carbonate: amoxycillin of at least 1.66.

-4-

Suitable ranges of molar ratios of sodium glycine carbonate: amoxycillin: citric acid are 1.5-4.5: 0.2-1: 1. The suitable molar ratio expressed above corresponds to a weight ratio sodium glycine carboante: amoxycillin: citric acid of 5 1.7-5.5: 0.4-1.9: 1.

For lower doses of amoxycillin, for example 500mg, 250mg and 125mg the levels of sodium ions is not excessive and the inclusion of potassium bicarbonate is not necessary.

10

Conventional excipients, such as colourings, fillers, diluents, sweeteners and flavourings may be added to the formulations, typically in an amount up to around 10% by weight, e.g. 1-7.5%. A suitable sweetener is aspartame.

15

The formulations are typically in the form of free flowing powders or granules, or tablets.

20

Soluble tablets may contain conventional water-soluble lubricants such as sodium lauryl sulphate or sodium benzoate, typically up to around 7.5% or less.

25

Alternatively tablets may be made using external lubrication on liquid-lubricated presses, or on double-sided presses where solid lubricant placebo compacts containing, for example, magnesium stearate are made on one side, continuously pre-lubricating the dies. The manufacturing method may be entirely conventional, e.g. formation of a granulate intermediate containing some or all of the milled components, followed by optionally blending with the other 30 components and then pressing into tablets.

35

Soluble tablets are preferably conventionally packaged in protective containers such as screw cap bottles, aluminium foil sachets, plastics or metal tubes, or aluminium blister packs. Soluble powders or granules are preferably conventionally packaged in individual aluminium foil

-5-

sachets, each containing a unit dose of the antibiotic. It may be appropriate to incorporate a desiccant in the packaging.

5 The amount of amoxycillin in a unit dose will depend on the infection to be treated and the assay of the amoxycillin. The unit-dose will be repeated according to the usual regime for amoxycillin treatments. Typically a unit dose may contain 3000, 875 or 125 mg of amoxycillin per tablet or 10 sachet, or an intermediate dose.

The invention also provides a formulation as defined above for use in the treatment of bacterial infections in humans or animals.

15

The invention also provides a method of treatment of bacterial infections in humans or animals which comprises administering to the human or animal patient a formulation as defined above in an antibacterially effective amount.

20

The invention also provides a process for the preparation of a pharmaceutical formulation which comprises admixing an amoxycillin hydrate and an effervescent couple, the couple comprising an acid component and an alkaline component which generates carbon dioxide on contact with water, the alkaline component of the couple being present in excess of the stoichiometric equivalent of the acid component.

The invention also provides a use, of an admixture of an amoxycillin hydrate and an effervescent couple, the couple comprising an acid component and an alkaline component which generates carbon dioxide on contact with water, the alkaline component of the couple being present in excess of the stoichiometric equivalent of the acid component, in the manufacture of a medicament for the treatment of bacterial infections.

-6-

The invention is illustrated by the following Examples.

Example 1

5 3g Dose Soluble Sachet

<u>Ingredients</u>	<u>g/dose</u>	<u>% w/w</u>
Amoxycillin trihydrate (as free acid)	3.000	22.5
10 Potassium bicarbonate	2.800	21.04
Sodium glycine carbonate	6.212	46.7
Citric acid	0.800	6.01
Aspartame	0.150	1.13
Sodium saccharin	0.040	0.30
15 Lemon juice flavour	0.220	1.65
Cinnamon flavour	0.085	0.64

Reconstitution: Add the contents of each sachet to 200mls of water and stir gently.

20

Manufacturing Process

The amoxycillin trihydrate was passed through an Apex 114 mill fitted with a 0.027 inch (0.686 mm) aperture screen 25 using hammers forward at 4590 rpm.

The potassium bicarbonate, sodium glycine carbonate, aspartame, dried saccharin sodium and citric acid were passed through a 30 mesh screen and placed in a blender 30 with the milled amoxycillin trihydrate. The mix was blended for 20 minutes at slow speed. The blend was then passed through a roller compactor, and the compact passed through an Apex 114 mill fitted with a 0.063 inch (1.6 mm) aperture screen, using knives forward at 2880 rpm, into a blender.

-7-

The flavours were screened through a 20 mesh screen into the blender, and the mix blended for 15 minutes at slow speed. The final mixture was filled into sachets at a weight calculated to deliver the required dose of amoxycillin.

5

Example 2

1g Dose Soluble Sachets

10 <u>Ingredients</u>	mg/ <u>sachet</u>	(% w/w)
Amoxycillin Trihydrate equivalent to Amoxycillin	875.0	19.06
15 free acid		
Potassium Clavulanate equivalent to Clavulanic acid	125.0	2.72
Potassium bicarbonate	930.0	20.26
Citric acid (anhydrous)	270.0	5.88
20 Aspartame	40.0	0.87
Sodium saccharin	10.4	0.23
Lemon dry flavour	73.0	1.59
Cinnamon flavour	28.0	0.61
Sodium glycine carbonate	2238.6	48.77

25

Manufacturing Process

The amoxycillin trihydrate was passed through an Apex 114 mill fitted with a 0.027 inch (0.686 mm) screen using 30 hammers forward at 4,600 rpm. All other ingredients were passed though a 30 mesh screen. The reduced amoxycillin trihydrate and other ingredients were blended in a suitably sized Y-cone blender for 20 minutes. The resultant mixture was compacted on a roller compactor, and the compact was 35 reduced to granules and classified.

-8-

Example 33.25g Dose Soluble Sachet

5

<u>Ingredients</u>	<u>mg/dose</u>	<u>% (w/w)</u>
Amoxycillin trihydrate	3000 (as free acid)	25.0
Potassium clavulanate	250 (as free acid)	2.08
Sodium glycine carbonate	4968	41.39
Potassium bicarbonate	2504	20.86
Citric acid anhydrous	640	5.33
Aspartame	150	1.25
Sodium saccharin	40	0.33
Golden syrup flavour	150	1.25
Banana flavour	300	2.5

Example 420 156.3mg Dose Soluble Tablet

<u>Ingredients</u>	<u>mg/tablet</u>	<u>% (w/w)</u>
Amoxycillin trihydrate	125.00 (as free acid)	10.43
Potassium clavulanate	31.25 (as free acid)	2.61
Sodium glycine carbonate	625.00	52
Citric acid anhydrous	200.00	16.69
Sodium benzoate	66.90	5.58
Aspartame	37.50	3.13
Golden syrup flavour	37.50	3.13
Banana flavour	75.00	6.26

-9-

This tablet is compressed on 9/16 inch (14.288 mm) bevel-flat punches.

Example 5

5

125mg Dose Soluble Tablets

<u>Ingredients</u>	<u>mg/tablet</u>	<u>% (w/w)</u>
10 Amoxycillin trihydrate	125.0 (as free acid)	18.89
Sodium glycine carbonate	406.3	61.39
Citric acid anhydrous	93.8	14.17
Aspartame	12.1	1.83
Lemon juice flavour	17.8	2.69
15 Cinnamon flavour	6.8	1.03

Manufacturing Process

The amoxycillin trihydrate was passed through an Apex 114 mill fitted with a 0.027 inch (0.686 mm) screen, hammers forward, at 7200 rpm into a blender. The citric acid was passed through an Apex 114 mill fitted with a 0.040 inch (1 mm) screen, hammers forward, at 7200 rpm into the blender. The other ingredients except for the flavours were passed 25 though a 30 mesh screen into the blender. The mix was blended for 20 minutes, and the blend slugged on one side of a Manesty BB4 double-sided press fitted with 1/2 inch (12.5 mm) round bevelled flat tooling. A lubricating mix consisting of 3% magnesium stearate in lactose was 30 compressed on the other side of the machine. The slugs were milled on an Apex 114 mill fitted with a 0.063 (1.6 mm) inch screen, knives forward at 2900 rpm. The flavours were passed through a 30 mesh screen and blended with the reduced slugs for 20 minutes. The blend was compressed on the 35 double-sided press fitted with the same tooling as used to prepare the slugs, and lubricated in the same manner.

-10-

Example 6

250mg Dose Soluble Tablets

5 250mg tablets were prepared by exactly doubling the quantities described in Example 5, and using an identical process except for replacing the $\frac{1}{2}$ inch (12.5 mm) punches by $\frac{5}{8}$ inch (15.875 mm) punches.

10 In the formulations of Examples 1-6 above the relative proportions of components are preferably maintained within \pm 10% of the stated quantities.

Claims

1. A pharmaceutical formulation comprising an amoxycillin hydrate and an effervescent couple, the couple comprising an acid component and an alkaline component, which generates carbon dioxide on contact with water, in which the alkaline component of the couple is present in excess of the stoichiometric equivalent of the acid component.

10

2. A pharmaceutical formulation according to claim 1 in which the amoxycillin hydrate is amoxycillin trihydrate and/or is in conjunction with a β -lactamase inhibitor.

15 3. A pharmaceutical formulation according to claim 2 in which a β -lactamase inhibitor is present and is clavulanic acid or a salt thereof, in a weight ratio of 12:1 to 1:1 amoxycillin hydrate : inhibitor.

20 4. A pharmaceutical formulation according to any one of the preceding claims in which the proportion of amoxycillin hydrate is 10 - 30% by weight.

25 5. A pharmaceutical formulation according to any one of the preceding claims in which the effervescent couple is selected from citric acid, tartaric acid or malic acid or mixtures thereof as acid component, and sodium bicarbonate, sodium glycine carbonate or sodium carbonate, or the corresponding potassium salts, or mixtures thereof as the 30 alkaline component.

6. A pharmaceutical formulation according to any one of the preceding claims which when made up into aqueous solution has a pH of not less than 8.

-12-

7. A pharmaceutical formulation according to any one of the preceding claims which contains 50 - 75 weight % of alkaline component.

5

8. A pharmaceutical formulation according to any one of the preceding claims in which the alkaline component is a 3 - 1.5 : 1 by weight mixture of sodium glycine carbonate or sodium bicarbonate : potassium bicarbonate.

10

9. A pharmaceutical formulation according to any one of the preceding claims which contains 2 - 25 weight % of the acid component.

15

10. A pharmaceutical formulation according to any one of the preceding claims containing a molar ratio of sodium glycine carbonate : amoxycillin : potassium bicarbonate : citric acid in the range 4-10 : 1- 3 : 5-10 : 1.

20

11. A pharmaceutical formulation according to claim 1 being a free flowing powder or granule formulation and having a composition within ± 10% of :

<u>Ingredient</u>	<u>% w/w</u>
Amoxycillin trihydrate as free acid	22.5
Potassium bicarbonate	21.04
Sodium glycine carbonate	46.7
Citric acid	6.01
Aspartame	1.13
Sodium saccharin	0.30
Lemon juice flavour	1.65
Cinnamon flavour	0.64

-13-

12. A pharmaceutical formulation according to claim 1
being a free flowing powder or granule formulation having a
composition within ± 10% of :

<u>5 Ingredients</u>	<u>% w/w</u>
Amoxycillin Trihydrate equivalent to Amoxycillin free acid	19.06
Potassium Clavulanate equivalent 10 to Clavulanic acid	2.72
Potassium bicarbonate	20.26
Citric acid (anhydrous)	5.88
Aspartame	0.87
Sodium saccharin	0.23
15 Lemon dry flavour	1.59
Cinnamon flavour	0.61
Sodium glycine carbonate	48.77

13. A pharmaceutical formulation according to claim 1
20 being a free flowing powder or granule formulation having a
composition within ± 10% of :

<u>Ingredients</u>	<u>% w/w</u>
25 Amoxycillin trihydrate as free acid	25.0
Potassium clavulanate as free acid	2.08
Sodium glycine carbonate	41.39
Potassium bicarbonate	20.86
Citric acid anhydrous	5.33
30 Aspartame	1.25
Sodium saccharin	0.33
Golden syrup flavour	1.25
Banana flavour	2.5

-14-

14. A pharmaceutical formulation according to claim 1
being a tablet formulation having a composition within $\pm 10\%$
of :

	<u>Ingredients</u>	<u>% w/w</u>
	Amoxycillin trihydrate as free acid	10.43
	Potassium clavulanate as free acid	2.61
10	Sodium glycine carbonate	52.16
	Citric acid anhydrous	16.69
	Sodium benzoate	5.58
	Aspartame	3.13
	Golden syrup flavour	3.13
15	Banana flavour	6.26

15. A pharmaceutical formulation according to claim 1
being a tablet formulation having a composition within $\pm 10\%$
of :

20

	<u>Ingredients</u>	<u>% w/w</u>
	Amoxycillin trihydrate as free acid	18.89
	Sodium glycine carbonate	61.39
25	Citric acid anhydrous	14.17
	Aspartame	1.83
	Lemon juice flavour	2.69
	Cinnamon flavour	1.03

30 16. A pharmaceutical formulation according to any one of
the preceding claims, containing a unit dose of amoxycillin
between 3000 and 125 mg.

-15-

17. A pharmaceutical formulation according to any one of the preceding claims, substantially as hereinbefore described in examples 1 - 6.

5 18. A pharmaceutical formulation according to any one of the preceding claims, for use in the treatment of bacterial infections in humans or animals.

19. A process for the preparation of a pharmaceutical formulation which comprises admixing an amoxycillin hydrate and an effervescent couple, the couple comprising an acid component and an alkaline component which generates carbon dioxide on contact with water, the alkaline component of the couple being in excess of the stoichiometric equivalent of 15 the acid component.

20. The use of an admixture of an amoxycillin hydrate and an effervescent couple, the couple comprising an acid component and an alkaline component which generates carbon dioxide on contact with water, the alkaline component of the couple being present in excess of the stoichrometric equivalent of the acid component, in the manufacture of a medicament for the treatment of bacterial infections.

25 21. A method of treatment of bacterial infections in humans or animals which comprises administering to a human or animal patient a formulation as claimed in any one of claims 1 - 18 in an antibacterially effective amount.

INTERNATIONAL SEARCH REP RT

International Application No PCT/GB 91/00516

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁵: A 61 K 9/46, A 61 K 31/43

II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System | Classification Symbols

IPC⁵

A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US, A, 4888177 (G. GERGELY) 19 December 1989 see the claims 1,3,10-12,15 --	1,4-5,11, 15,19-20
A	EP, A, 0207041 (GALEPHAR) 30 December 1986 see claims 1,8-9,20,22-24; page 7, line 20; page 9, lines 18-21; page 17, example 4 --	1,4-5,11, 15,19-20
A	DE, A, 2020893 (BIOCHEMIE) 19 November 1970 see the claims 1,3-4,6,8-11; page 4, lines 16-17 cited in the application --	1,4-5,11, 15,19-20
A.	EP, A, 0080862 (BEECHAM) 8 June 1983 see the claims cited in the application --	1-4,11,16- 20 . / .

* Special categories of cited documents: to

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"C" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report

2nd July 1991 | 14 AUG 1991

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category	Citation of Document, ¹³ with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP, A, 0281200 (GIST-BROCADES) 7 September 1988 see claims 1,4,8,11-12; page 4, lines 43-47 cited in the application -----	1-4,11,16- 20

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9100516
SA 46303

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 06/08/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4888177	19-12-89	DE-A-	3440288	07-05-86
		AU-B-	576399	25-08-88
		AU-A-	4931885	15-05-86
		AU-B-	584154	18-05-89
		AU-A-	5199086	03-06-86
		CA-A-	1254143	16-05-89
		WO-A-	8602834	22-05-86
		EP-A, B	0181564	21-05-86
		EP-A, B	0232277	19-08-87
		JP-A-	61115023	02-06-86
		JP-T-	62501210	14-05-87
		US-A-	4762702	09-08-88
EP-A- 0207041	30-12-86	LU-A-	85943	13-01-87
DE-A- 2020893	19-11-70	AT-A-	307616	15-04-73
		BE-A-	749864	30-10-70
		FR-A, B	2043500	19-02-71
		GB-A-	1300998	29-12-72
		NL-A-	7006040	04-11-70
EP-A- 0080862	08-06-83	AU-A-	9103782	09-06-83
		JP-C-	1580055	13-09-90
		JP-B-	2006332	08-02-90
		JP-A-	58109419	29-06-83
EP-A- 0281200	07-09-88	AU-B-	603870	29-11-90
		AU-A-	1252088	01-09-88
		JP-A-	63301820	08-12-88
		US-A-	4950484	21-08-90